

RESEARCH ON SKELETAL GROWTH AND DEVELOPMENT

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P.T.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute for Child Health and Human Development

National Institute of Dental Research

National Institute of Diabetes, Digestive, and Kidney Diseases

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute for Child Health and Human Development (NICHD), the National Institute of Dental Research (NIDR), and the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) encourage investigator-initiated research grant applications to study axial, appendicular, and craniofacial skeletal growth and development. The purpose of this Skeletal Growth and Development Program Announcement (PA) is to inform the scientific community of our interests, and to stimulate and foster a wide range of basic, translational and patient-oriented clinical studies, in skeletal growth and development. Applications are encouraged to study skeletal growth and development from the perspectives of mechanisms of pattern formation, cartilage induction, endochondral ossification, intramembranous bone formation, biomechanics, and the clinical treatment of the resulting disorders.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, Research on Skeletal Growth and Development, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications from minority individuals, women, and persons with disabilities are encouraged.

MECHANISM OF SUPPORT

The mechanism of support will be the research project grant (R01); applicants are advised to contact the program officials listed under INQUIRIES for information. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Awards will be administered under PHS grants policy as stated in the Public Health Service Grants Policy statement (April 1, 1994).

RESEARCH OBJECTIVES

Background

Disturbances in skeletal growth and development cause a wide variety of clinical disorders. These disorders can involve any part of the musculoskeletal system. They can be localized to a specific anatomic region, or can extend throughout the musculoskeletal system. They vary in severity from asymptomatic lesions to lethal, generalized skeletal dysplasias. Representative examples include, but are not limited to, joint dysplasias, slipped capital femoral epiphysis, scoliosis, clubfoot, spina bifida, and failure of normal bone growth manifested as dwarfism. The disturbances that lead to joint dysplasias and malformations may lead to the early onset of degenerative osteoarthritis, which affects approximately 500,000 people in the United States. Adolescent idiopathic scoliosis, one type of this condition, has a prevalence of 25 per 1,000 in the population. As a group, these disturbances have significant economic and human impact, as relates to functional limitations and the potential for a reduced quality of life.

Recently, there have been significant scientific advances defining the sequential expression of genes responsible for the synthesis of matrix molecules and formation and growth of the musculoskeletal system. Additional observations have identified the critical roles of certain cytokines in controlling cell proliferation and matrix synthesis. However, few of these discoveries have been translated into treatment advances of the multiple clinical conditions that result from disturbances in molecular mechanisms. Dramatic improvement in treatment may require a new

level of understanding, one that incorporates the combined efforts of cell and molecular biologists, morphologists, clinicians, and bioengineers.

The current PA indicates our continued interest in skeletal growth and development, and is the direct outgrowth of a NIAMS, NICHD, American Academy of Orthopaedic Surgeons, and Orthopaedic Research and Education Foundation-sponsored workshop on the status and future research directions on Skeletal Growth and Development, held in May 1997. The specific aims of this multidisciplinary workshop were to: (1) define the current knowledge of skeletal morphogenesis and growth, including the formation of the bony skeleton and the synovial joints, and current knowledge of disturbances of skeletal morphogenesis and growth; (2) identify potential applications of basic knowledge of skeletal growth, development and morphogenesis to clinical problems; (3) identify future research directions that will advance understanding of skeletal growth, development, and morphogenesis, and the relationship of disturbances in these processes to the development of clinical disorders; and (4) to identify future research directions that will increase the ability to maintain and regenerate musculoskeletal tissues. To accomplish these aims, a multidisciplinary group of basic scientists and clinicians were assembled to define our current knowledge and to identify future cross-cutting, research directions. A more detailed description of the proceedings and suggested research topics can be found in *Skeletal Growth and Development: Clinical Issues and Basic Science Advances*, which can be obtained from the American Academy of Orthopaedic Surgeons, Chicago, Illinois. Although not the subject of the referenced meeting, it is in the interests of the NIH to include in this Program Announcement related research in the areas of craniofacial skeletal growth and development.

Scope of Research Sought

Through the use of this PA, the sponsoring Institutes anticipate the receipt of a broad range of applications targeted, but not limited, to the following areas related to axial, appendicular, and craniofacial skeletal growth and development:

- o Mechanisms of pattern formation, cartilage induction, endochondral ossification, and intramembranous bone formation Control of angiogenesis in bone morphogenesis and growth.
- o Mechanism(s) by which cells are responsive to electrical or other physical stimuli.
- o Regulation and importance of programmed cell death in the maintenance and pathology of skeletal tissues.
- o Nature and functional consequences of cell-cell and cell-matrix interactions during skeletogenesis.

- o Cellular and molecular differences between intramembranous and endochondral bone formation.
- o Effects of distraction and compression on growth plate function.
- o Identification and role of growth factors, transcription factors, etc. in the initiation of cartilaginous rudiment formation.
- o Regulation of chondrocyte maturation in the growth plate.
- o Mechanisms of signal transduction in the growth plate.
- o Mechanisms of fracture healing.
- o Developmental processes influencing bone healing or remodeling. Role of the joint interzone in endochondral bone development.
- o Identification of patterning defects resulting in skeletal abnormalities.
- o Development of improved animal models to study disturbances of axial, appendicular, and craniofacial skeletal morphogenesis and growth.
- o Role of growth factors in the development of peak skeletal mass and the healing of articular cartilage.
- o Role of skeletal factors in tooth eruption.

Biomechanical and clinical applications

- o Role of joint congruence and stability in the development of synovial joints.
- o Factors responsible for bar formation in the physis, and for its successful excision.
- o Effects of growth on the scoliotic spine following posterior spinal fusion.
- o Pathophysiology of hip dysplasia and dislocation (e.g., joint congruence and stability in developing synovial joints) and their surgical management, to justify treatment approaches.
- o Mechanisms of manipulative, bracing and surgical corrections of axial, appendicular, and craniofacial skeletal deformities, the stability of effects over time, and the effectiveness/outcomes of such treatments.

No priority has been established among the research suggestions presented.

Applications are encouraged in any scientifically meritorious research area related to skeletal growth and development. Research applications are encouraged from all basic science disciplines pertinent to this area, as well as the various clinical specialties providing health care services for these patients.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving

human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994 available on the web at the following URL address: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.5/95) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC-7910, Bethesda, MD 20892-7910 telephone: (301) 435-0714; Email: GrantsInfo@nih.gov. The title and number of the program announcement must be typed in Section 2 on the face page of the application.

The completed original application and five legible copies must be sent or delivered to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications that are complete will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

(1) Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation. Does the project employ novel concepts, approaches, or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, and in accordance with NIH policy, all applications will also be reviewed with respect to the following:

(1) The adequacy of plans to include both genders, minorities, and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

(2) The reasonableness of the proposed budget and duration in relation to the proposed research.

(3) The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be considered in making funding decisions: quality of the proposed project as determined by peer review; availability of funds; and program relevance and balance among research areas of the program announcement.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No.93.846 Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78th Congress, as amended, 42 USC 241) and administered under PHS grant policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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